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Visible Light-Promoted Synthesis of Spiroepoxy Chromanone Derivatives via a Tandem Oxidation/Radical Cyclization/Epoxidation Process

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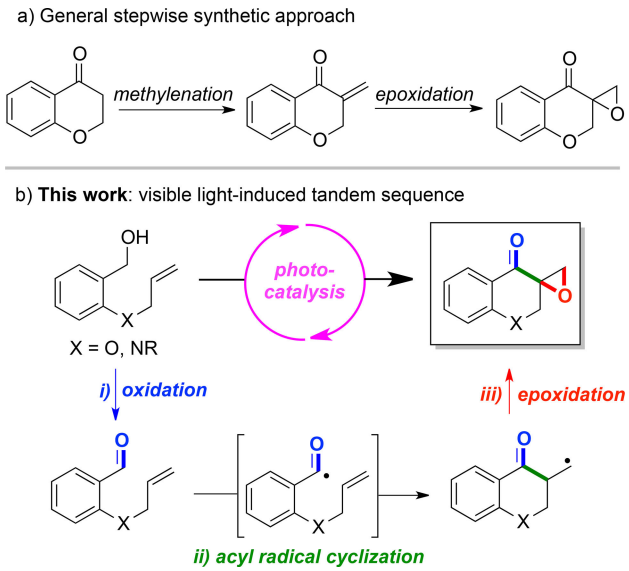
Abstract: A highly efficient and straightforward approach for the synthesis of spiroepoxy chroman-4-one derivatives was developed using a visible light-enabled tandem radical strategy. The reaction is initiated by the formation of an acyl radical that undergoes intramolecular radical cyclization and epoxidation. The optimal result was obtained with 1 mol% of $Ru(bpy)_3Cl_2·6H_2O$, TBHP, and K_2CO_3 in *i*-PrOAc at room temperature with irradiation from a blue LED. This unprecedented tandem approach utilizes a broad range of substrates, and provides a convenient and powerful synthetic tool for accessing the synthetically useful spiroepoxy chroman-4-ones and their nitrogen-containing derivatives.

Keywords: acyl radical; radical cyclization; visible light; tandem; photocatalysis

The chroman-4-one scaffolds constitute an important class of naturally occurring compounds and privileged scaffolds in medicinal chemistry.[1] Along these lines, a series of synthetic methods to synthesize these scaffolds have been developed using various catalytic systems.[2] The spiroepoxy chroman-4-one moiety is also extremely fascinating because of its versatility in further synthetic transformation, allowing it to be converted into a diverse range of useful molecular entities.[3] Despite these important contributions, existing methods for preparing this motif suffer from multiple steps, and harsh reaction conditions.[4] In this context, a more straightforward approach for synthesizing structurally diverse spiroepoxy chroman-4-ones under mild reaction conditions is a topic of considerable importance.[5]

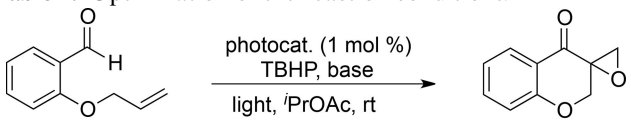
Strategies using visible light-driven photoredox catalysis emerge as the promising alternative to the existing methods, as they are powerful and environmentally benign tools for synthesizing various compounds under mild conditions.[6,7] We were intrigued by the possibility of developing photochemical reactions by employing a visible light-mediated protocol and combining a multistep sequence to construct the spiroepoxy chroman-4-one skeleton. Mechanistically, both the oxidation of benzylic alcohol[8] and the generation of the acyl radical are believed to proceed by the action of peroxy radicals, which would set the stage for intramolecular radical cyclization with internal alkenes.[9] Therefore, we envisioned that the aldehyde group generated in situ as a result of visible light-mediated oxidation of benzylic alcohol could be further utilized for spontaneous intramolecular acyl radical cyclization with internal olefins via a photoredox process. Subsequently, the generated β-peroxy intermediate might further undergo a base-assisted epoxidation to install a spiroepoxy group in the chroman-4-one skeleton. If successful, this visible light-enabled tandem radical strategy is highly desirable and efficient from the perspectives of green process. Herein, we present the first example of a visible light photocatalyzed tandem synthesis of diverse spiroepoxy chroman-4-one derivatives and their nitrogen-containing counterparts (Scheme 1). Moreover, mild room temperature conditions are sufficient for the construction of the scaffolds in the overall reaction process.

To corroborate this hypothesis, the feasibility of using a photoreaction to convert aldehyde substrate **1a** into spiroepoxy chroman-4-one **2a** via a radical-based cyclization was initially investigated, and selected data are listed in Table 1. After screening some potential catalytic systems, the corresponding product **2a** was obtained upon irradiation of **1a** in the presence of 1 mol% of $Ir(ppy)_3$ at room temperature under irradiation by a household fluorescent light (Table 1, entries 3 and 4), thus highlighting that the overall process was operating effectively. It was



Scheme 1. Synthetic approach to the spiroepoxy chroman-4-ones and their nitrogen-containing derivatives via a visible light-induced tandem oxidation/radical cyclization/epoxidation sequence.

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

entry	Photocat (1 mol%)	base (3 quiv)	light source	yield (%)
1	$Ir(ppy)_3$	KO^{t}Bu	23 W CFL	trace
2	$Ir(ppy)_3$	DBU	23 W CFL	–
3	$Ir(ppy)_3$	Cs_2CO_3	23 W CFL	25
4	$Ir(ppy)_3$	K_2CO_3	23 W CFL	39
5[b]	$Ir(ppy)_3$	–	23 W CFL	–
6	$[Ir(dF(CF_9)ppy)_2(bpy)]PF_6$	K_2CO_3	23 W CFL	64
7	$Ru(bpz)_3PF_6$	K_2CO_3	23 W CFL	47
8	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2CO_3	23 W CFL	72
9	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_3PO_4	23 W CFL	65
10	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	Cs_2CO_3	23 W CFL	44
11	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2CO_3	blue LED	74
12	–	K_2CO_3	blue LED	–
13	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	K_2CO_3	–	trace

[a] Procedure A: **1** (1.0 equiv), photocatalyst (1.0 mol%), TBHP (5.0 equiv), and base (3.0 equiv) in *i*-PrOAc (0.1 M) at rt under N_2 for 24 h with light irradiation. ^{1}H NMR yield using an internal standard.

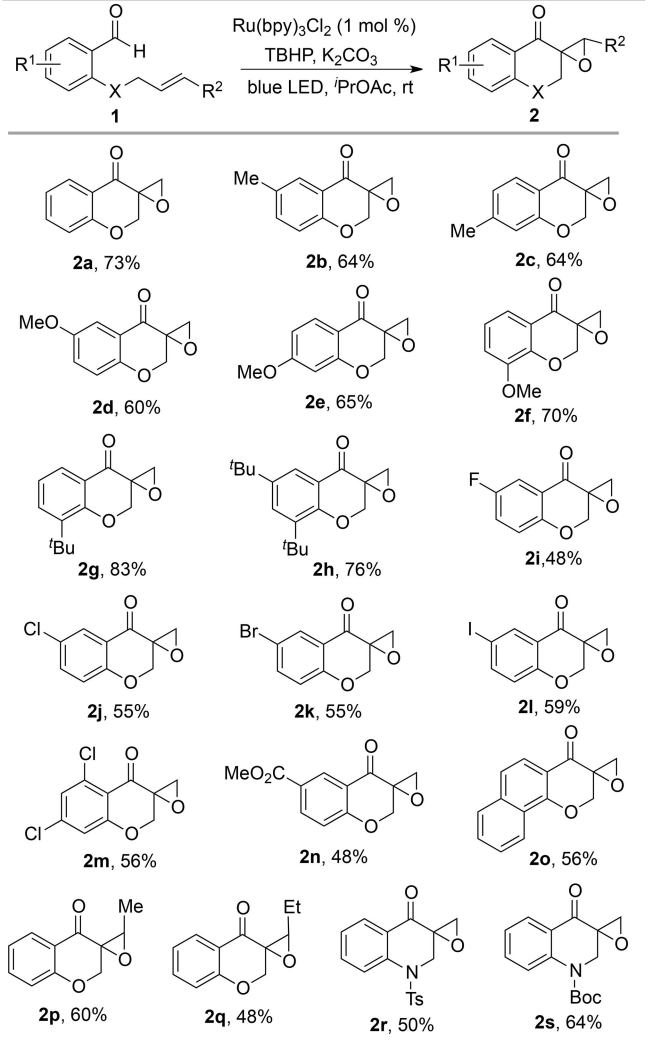
[b] β-Peroxy ketone intermediate was isolated in 42% yield with 40% recovery of starting material **1a**. TBHP = *tert*-butyl hydrogen peroxide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

determined that the use of base promoted the formation of **2a**, and the intermediate β-peroxy ketone was detected in the absence of base, indicating that β-peroxy ketone is a key intermediate in the reactions. (entry 5). Among the bases screened, K_2CO_3 was most effective in terms of overall conversion. With this encouraging preliminary result, thorough screening of reaction media with photocatalysts was conducted with the goal of optimizing the reaction outcome. More promising results were obtained using $Ru(bpy)_3Cl_2{\cdot}6H_2O$, which afforded **2a** in 72% yield under an N_2 balloon (entry 8). Further investigations revealed that *i*-PrOAc was most efficient in this reaction. Various light sources were further screened, and the use of a blue LED resulted in an improvement in yield (entry 11). Subsequent control experiments confirmed the essential role of visible light and the photocatalyst in this reaction (entries 12, and 13).

The optimal conditions were then applied to a variety of substrates to demonstrate the utility and generality of this method, the results of which are summarized in Table 2. We were pleased to observe that by this catalytic method, spiroepoxy chroman-4-one scaffolds could easily be prepared with either electron-rich or electron-deficient substituents (methyl, methoxy, fluoro, chloro, bromo, and ester) with the desired products being generated in moderate to good yields at room temperature. Notably, halides such as Cl, Br and I were well tolerated under the reaction conditions and provided the desired products (**2j, 2k**, and **2l**), thereby facilitating further functionalization. In a similar fashion, substrates bearing substituted alkenes are viable precursors for products **2p** and **2q**. Importantly, expanding the scope from allyloxy- to allylamino-compounds was also possible and gave rise to the corresponding spiroepoxy enaminone products (**2r** and **2s**), thereby significantly expanding the scope and synthetic utility of this reaction. The structure of the product **2d** was unambiguously confirmed by X-ray diffraction.[10]

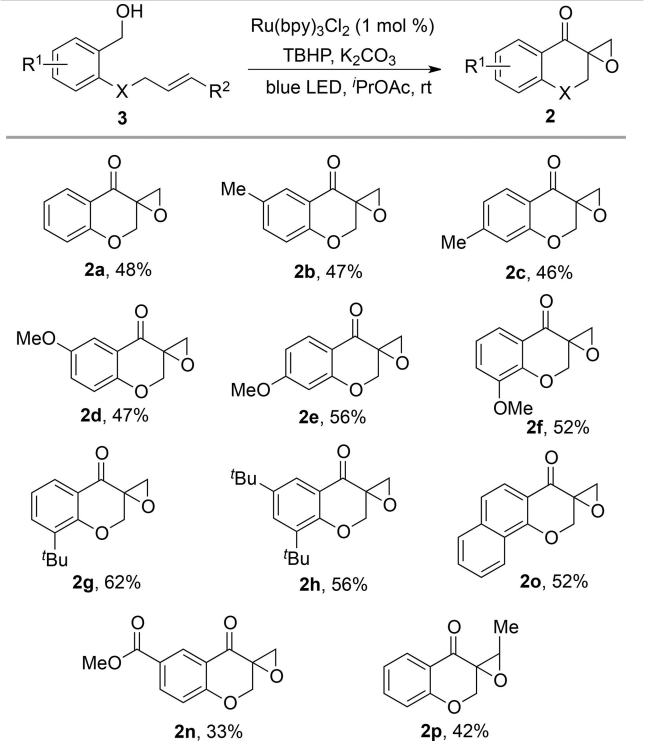
Encouraged by the above results, we next turned our attention to the proposed three-step tandem process mentioned previously by investigating the optimal reaction conditions under blue LED irradiation at room temperature. To this end, we screened a number of reaction conditions. When the amount of TBHP was increased to 8.0 equiv, the benzylic alcohol was completely converted to the corresponding aldehyde, and overall reaction yields improved. When alcohol **3** was subjected to the optimized conditions, the desired sequential oxidation/intramolecular radical cyclization /epoxidation process proceeded, thus exhibiting that this method allows the synthesis of spiroepoxy chroman-4-one derivatives. Subsequently, we examined the scope of this protocol with respect to the substituents and were delighted to observe that a

Table 2. Substrate scope of intramolecular radical cyclization/epoxidation reactions.[a]

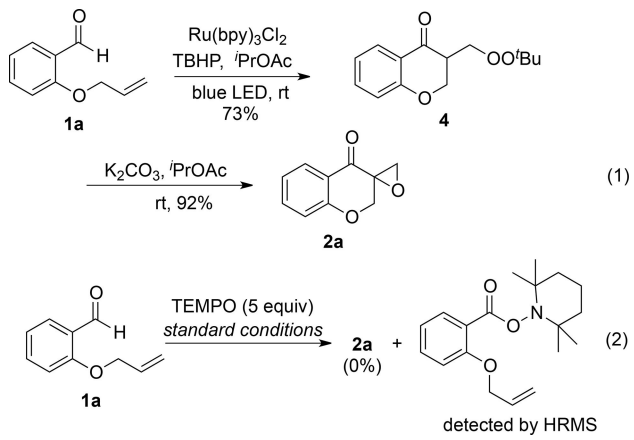


[a] **1** (0.20 mmol, 1.0 equiv), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1.0 mol%), TBHP (5.0 equiv), and K_2CO_3 (3.0 equiv) in *i*-PrOAc (0.1 M) at rt under N_2 for 20–24 h with light irradiation using a blue LED. Yields of isolated products.

Table 3. Substrate scope of the tandem process involving oxidation/intramolecular radical cyclization/epoxidation.[a]



[a] Procedure B: **3** (1.0 equiv), $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (1.0 mol%), TBHP (8.0 equiv), and K_2CO_3 (3.0 equiv) in *i*-PrOAc (0.1 M) at rt under N_2 for 30–36 h with light irradiation using blue LED. Yields of isolated products.

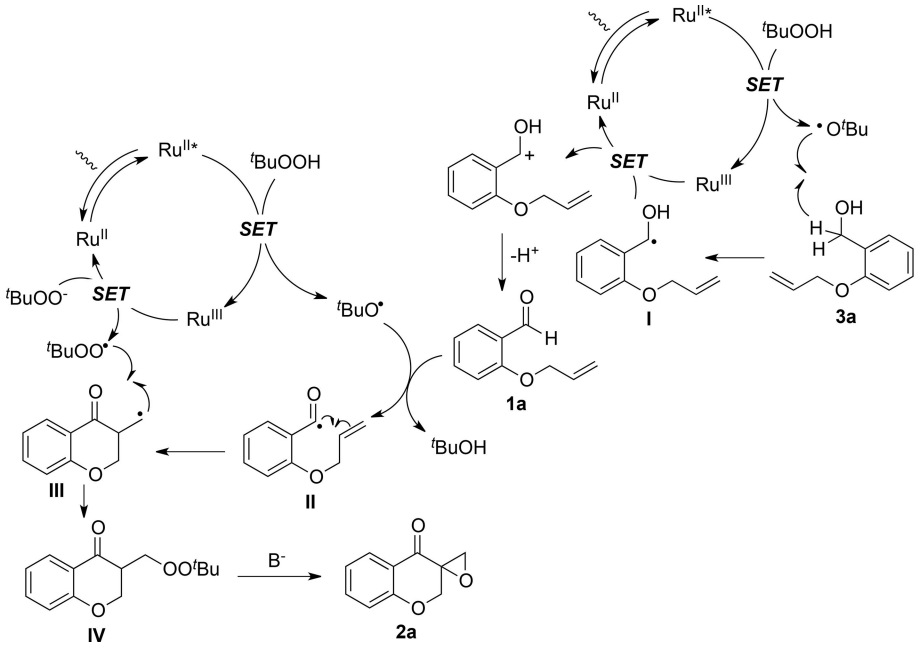


Scheme 2. Control experiments.

range of substrates were tolerated in this tandem process and successfully afforded the corresponding products, as shown in Table 3.

When aldehyde **1a** was subjected to the standard reaction conditions without adding base, β-peroxy ketone **4** was obtained in 71% yield. The α-carbonyl epoxide **2a** was then synthesized through a base-induced epoxidation of the separated β-peroxy ketone **4** (Scheme 2, eq 1).[9a,11] Next, the complete quenching of reactivity in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) supports the involvement of a radical intermediate (Scheme 2, eq 2).

A plausible mechanism for the visible light mediated tandem process is depicted in Scheme 3. The photoexcited Ru(II)* species under blue LED irradiation may act as a single electron transfer (SET) reagent. The catalytic process can be initiated by oxidation of the hydroxyl group by the *tert*-butoxy radical that is formed by SET-induced scission of the weak O–O bond of TBHP.[12] The resulting aldehyde **1a** is then engaged in the second catalytic cycle, and its acyl radical species **II** is presumably generated by



Scheme 3. Proposed mechanism of the present tandem catalysis

hydrogen abstraction of the aldehydic hydrogen. Afterward, intramolecular cyclization of the acyl radical **II** with the internal olefin gives rise to the radical intermediate **III**, which undergoes radical coupling with a peroxy radical as the Li's group reported.[9a] Finally, the base-assisted epoxidation of the resulting β-peroxy intermediate **IV** yields product **2a**.

In summary, we developed a straightforward and efficient tandem reaction for the direct construction of spiroepoxy chroman-4-ones with light irradiation using a blue LED under mild reaction conditions. During the reaction, the aldehyde generated in situ from the benzyl alcohol could further undergo visible light-mediated internal radical cyclization and epoxidation. The present strategy allows the rapid generation of valuable and synthetically useful spiroepoxy chroman-4-ones and their nitrogen-containing derivatives.

Experimental Section

General Procedure

Procedure A: Reactions were conducted in test tube sealed with rubber septa. The mixture of aldehyde **2a** (32.4 mg, 0.20 mmol), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1.5 mg, 0.002 mmol), *tert*-butyl hydroperoxide (5.5 M in decane, 0.18 mL, 1.0 mmol) and K_2CO_3 (82.9 mg, 0.60 mmol) were combined in *i*-PrOAc (2.0 mL) under N_2 atmosphere. The mixture was placed in the irradiation apparatus equipped with a blue LED. The resulting mixture was stirred at room temperature. The reaction mixture was monitored by TLC using 91% *n*-hexane and 9% ethyl acetate as the mobile phase. After 24 h, the reaction mixture was diluted with ethyl acetate (25 mL x 3) and washed with brine (40 mL). The organic layer was dried over Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate = 10:1) to give the desired product compound **2a** (25.7 mg, 73%) as a white solid.

Procedure B: Reactions were conducted in test tube sealed with rubber septa. The mixture of alcohol **3a** (32.8 mg, 0.20 mmol), $Ru(bpy)_3Cl_2{\cdot}6H_2O$ (1.5 mg, 0.002 mmol), *tert*-butyl hydroperoxide (5.5 M in decane, 0.29 mL, 1.6 mmol) and K_2CO_3 (83.1 mg, 0.60 mmol) were combined in *i*-PrOAc (2.0 mL) under N_2 atmosphere. The mixture was placed in the irradiation apparatus equipped with a blue LED. The resulting mixture was stirred at room temperature. The reaction mixture was monitored by TLC using 91% hexane and 9% ethyl acetate as the mobile phase. After 36 h, the reaction mixture was diluted with ethyl acetate (25 mL x 3) and washed with brine (40 mL). The organic layer was dried over Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 10:1) to give the desired product compound **2a** (16.8 mg, 48%) as a white solid.

Acknowledgements

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[10] CCDC-1569248 contains the supplementary crystallographic data for compound **2d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See the Supporting Information for details.

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COMMUNICATIONS

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